ARANESP ä
(darbepoetin alfa)
For Injection

DESCRIPTION

Aranesp™ is an erythropoiesis stimulating protein, closely related to erythropoietin, that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp™ is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3 chains (Egrie 2001). The 2 additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,000 to 37,000 daltons. Aranesp™ is formulated as a sterile, colorless, preservative-free protein solution for intravenous (IV) or subcutaneous (SC) administration.

Single-dose vials are available containing 25, 40, 60, 100, 150, 200, 300, or 500 mcg of Aranesp™. Two formulations contain excipients as follows:

Polysorbate solution contains 0.05 mg polysorbate 80, 2.12 mg sodium phosphate monobasic monohydrate, 0.66 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (per 1 mL) at pH 6.2 ± 0.2.

Albumin solution contains 2.5 mg albumin (human), 2.23 mg sodium phosphate monobasic monohydrate, 0.53 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (per 1 mL) at pH 6.0 ± 0.3.

CLINICAL PHARMACOLOGY

Mechanism of Action

Aranesp™ stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. In responding to hypoxia, erythropoietin interacts with progenitor stem cells to increase red cell production. Production of endogenous erythropoietin is impaired in patients with chronic renal failure (CRF), and erythropoietin deficiency is the primary cause of their anemia. Increased hemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment with Aranesp™ (see *DOSAGE AND ADMINISTRATION: Dose Adjustment*). In patients with cancer receiving concomitant chemotherapy, the etiology of anemia is multifactorial.

Pharmacokinetics

The pharmacokinetics of Aranesp™ were studied in patients with chronic renal failure and cancer patients receiving chemotherapy.

Over the therapeutic range of 0.45 to 4.5 mcg/kg, pharmacokinetic measures (Cmax, half-life, AUC) were linear with respect to dose and no evidence of accumulation was observed beyond an expected < 2-fold increase in blood levels when compared to the initial dose.

Following subcutaneous (SC) administration, absorption is slow and rate limiting. The observed half-life in CRF patients, which reflected the rate of absorption, was 49 hours (range: 27 to 89 hours). Following IV administration to these patients, Aranesp™ serum concentration-time profiles are biphasic, with a distribution half-life of approximately 1.4 hours and the mean terminal half-life of 21 hours. Post SC administration, CRF patients' peak concentrations occur at 34 hours (range: 24 to 72 hours) whereas cancer patients' peak concentrations are at 90 hours (range: 71 to 123 hours).

When administered by IV administration, the terminal half-life of Aranesp™ is approximately 3-fold longer than Epoetin alfa. The bioavailability of Aranesp™ as measured in CRF patients after SC administration is 37% (range: 30% to 50%).

CLINICAL STUDIES

Throughout this section of the package insert, the Aranesp™ study numbers associated with the nephrology and cancer clinical programs are designated with the letters "N" and "C", respectively.

Chronic Renal Failure Patients

The safety and effectiveness of Aranesp™ have been assessed in multicenter studies. Two studies evaluated the safety and efficacy of Aranesp™ for the correction of anemia in adult patients with CRF, and 2 studies assessed the ability of Aranesp™ to maintain hemoglobin concentrations in adult patients with CRF who had been receiving other recombinant erythropoietins.

De Novo Use of Aranesp ä

In 2 open-label studies, Aranesp™ or Epoetin alfa were administered for the correction of anemia in CRF patients who had not been receiving prior treatment with exogenous erythropoietin. Study N1 evaluated CRF patients receiving dialysis; Study N2 evaluated patients not requiring dialysis (predialysis patients). In both studies, the starting dose of Aranesp™ was 0.45 mcg/kg administered once weekly. The starting dose of Epoetin alfa was 50 U/kg 3 times weekly in Study N1 and 50 U/kg twice weekly in Study N2. When necessary, dosage adjustments were instituted to maintain hemoglobin in the study target range of 11 to 13 g/dL. (Note: The recommended hemoglobin target is lower than the target range of these studies. See *DOSAGE AND ADMINISTRATION: General* for

recommended clinical hemoglobin target.) The primary efficacy endpoint was the proportion of patients who experienced at least a 1.0 g/dL increase in hemoglobin concentration to a level of at least 11.0 g/dL by 20 weeks (Study N1) or 24 weeks (Study N2). The studies were designed to assess the safety and effectiveness of Aranesp™, but not to support conclusions regarding comparisons between the two products.

In Study N1, the hemoglobin target was achieved by 72% (95% CI: 62%, 81%) of the 90 patients treated with Aranesp™ and 84% (95% CI: 66%, 95%) of the 31 patients treated with Epoetin alfa. The mean increase in hemoglobin over the initial 4 weeks of Aranesp™ treatment was 1.10 g/dL (95% CI: 0.82 g/dL, 1.37 g/dL).

In Study N2, the primary efficacy endpoint was achieved by 93% (95% CI: 87%, 97%) of the 129 patients treated with Aranesp™ and 92% (95% CI: 78%, 98%) of the 37 patients treated with Epoetin alfa. The mean increase in hemoglobin from baseline through the initial 4 weeks of Aranesp™ treatment was 1.38 g/dL (95% CI: 1.21 g/dL, 1.55 g/dL).

Conversion From Other Recombinant Erythropoietins

Two studies (Studies N3 and N4) were conducted in adult patients with CRF who had been receiving other recombinant erythropoietins and compared the abilities of Aranesp™ and other erythropoietins to maintain hemoglobin concentrations within a study target range of 9 to 13 g/dL. (Note: The recommended hemoglobin target is lower than the target range of these studies. See *DOSAGE AND ADMINISTRATION: General* for recommended clinical hemoglobin target.) CRF patients who had been receiving stable doses of other recombinant erythropoietins were randomized to Aranesp™, or to continue with their prior erythropoietin at the previous dose and schedule. For patients randomized to Aranesp™, the initial weekly dose was determined on the basis of the previous total weekly dose of recombinant erythropoietin. Study N3 was a double-blind study conducted in North America, in which 169 hemodialysis patients were randomized to treatment with Aranesp™ and 338 patients continued on Epoetin alfa. Study N4 was an open-label study conducted in Europe and Australia in which 347 patients were randomized to treatment with Aranesp™ and 175 patients were randomized to continue on Epoetin alfa or Epoetin beta. Of the 347 patients randomized to Aranesp™, 92% were receiving hemodialysis and 8% were receiving peritoneal dialysis.

In Study N3, a median weekly dose of 0.53 mcg/kg Aranesp™ (25^{th}, 75^{th} percentiles: 0.30, 0.93 mcg/kg) was required to maintain hemoglobin in the study target range. In Study N4, a median weekly dose of 0.41 mcg/kg Aranesp™ (25^{th}, 75^{th} percentiles: 0.26, 0.65 mcg/kg) was required to maintain hemoglobin in the study target range.

Cancer Patients Receiving Chemotherapy

The safety and effectiveness of Aranesp™ in reducing the requirement for red blood cell (RBC) transfusions in patients undergoing chemotherapy were assessed in a randomized, placebo-controlled, double-blind, multinational study (C1). This study was conducted in anemic (Hgb = 11 g/dL) patients with advanced, small cell or non-small cell lung cancer, who received a platinum-containing chemotherapy regimen. Patients were randomized to receive Aranesp™ 2.25 mcg/kg (n = 156) or placebo (n = 158) administered as a single weekly SC injection for up to 12 weeks. The dose was escalated to 4.5 mcg/kg/week at week six, in subjects with an inadequate response to treatment, defined as less than 1 g/dL hemoglobin increase. There were 67 patients in the Aranesp™ arm who had their dose increased from 2.25 to 4.5 mcg/kg/week, at any time during the treatment period.

Efficacy was determined by a reduction in the proportion of patients who were transfused over the 12 week treatment period. A significantly lower proportion of patients in the Aranesp™ arm, 26% (95% CI: 20, 33) required transfusion compared to 60% (95% CI: 52, 68) in the placebo arm (Kaplan-Meier estimate of proportion; $p < 0.001$ by Cochran - Mantel - Haenszel test). Of the 67 patients who received a dose increase, 28% had a 2 g/dL increase in hemoglobin over baseline, generally occurring between weeks 8 to 13. Of the 89 patients who did not receive a dose increase, 69% had a 2 g/dL increase in hemoglobin over baseline, generally occurring between weeks 6 to 13.

Studies were conducted that evaluated doses of Aranesp™ ranging from 0.5 mcg/kg to 8.0 mcg/kg administered weekly. Data from these studies indicate that there is a dose response relationship with respect to hemoglobin response. The minimally effective starting dose with respect to reducing transfusion requirements was 1.5 mcg/kg/week with a plateau observed at 4.5 mcg/kg/week.

INDICATIONS AND USAGE

Aranesp™ is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis, and for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

CONTRAINDICATIONS

Aranesp™ is contraindicated in patients with:

- Uncontrolled hypertension
- Known hypersensitivity to the active substance or any of the excipients

WARNINGS

Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin

Aranesp™ and other erythropoietic therapies may increase the risk of cardiovascular events, including death. The higher risk of cardiovascular events may be associated with higher hemoglobin and/or higher rates of rise of hemoglobin. The hemoglobin level should be managed carefully to avoid exceeding a target level of 12 g/dL.

In a clinical trial of Epoetin alfa (rHuEPO) treatment in hemodialysis patients with clinically evident cardiac disease, patients were randomized to a target hemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL (Besarab 1998). Higher mortality (35% versus 29%) was observed in the 634 patients randomized to a target hemoglobin of 14 g/dL than in the 631 patients assigned a target hemoglobin of 10 g/dL. The reason for the increased mortality observed in this study is unknown; however, the incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dL.

In patients treated with Aranesp™ or other recombinant erythropoietins in Aranesp™ clinical trials, increases in hemoglobin greater than approximately 1.0 g/dL during any 2-week period were associated with increased incidence of cardiac arrest, neurologic events (including seizures and stroke), exacerbations of hypertension, congestive heart failure, vascular thrombosis/ischemia/infarction, acute myocardial infarction, and fluid overload/edema. It is recommended that the dose of Aranesp™ be decreased if the hemoglobin increase exceeds 1.0 g/dL in any 2-week period, because of the association of excessive rate of rise of hemoglobin with these events.

Hypertension

Patients with uncontrolled hypertension should not be treated with Aranesp™; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anemia with Aranesp™ or Epoetin alfa. In Aranesp™ clinical trials, approximately 40% of patients with CRF required initiation or intensification of antihypertensive therapy during the early phase of treatment when the hemoglobin was increasing. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with Aranesp™ or Epoetin alfa.

Special care should be taken to closely monitor and control blood pressure in patients treated with Aranesp™. During Aranesp™ therapy, patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by pharmacologic or dietary measures, the dose of Aranesp™ should be reduced or withheld (see *DOSAGE AND ADMINISTRATION: Dose Adjustment*). A clinically significant decrease in hemoglobin may not be observed for several weeks.

Seizures

Seizures have occurred in patients with CRF participating in clinical trials of Aranesp™ and Epoetin alfa. During the first several months of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of Aranesp™ be decreased if the hemoglobin increase exceeds 1.0 g/dL in any 2-week period.

Thrombotic Events

An increased incidence of thrombotic events has been observed in patients treated with erythropoietic agents. In patients with cancer who received Aranesp™, pulmonary emboli, thrombophlebitis and thrombosis occurred more frequently than in placebo controls (see *ADVERSE REACTIONS: Cancer Patients Receiving Chemotherapy, Table 4*).

Pure Red Cell Aplasia

Pure red cell aplasia (PRCA), in association with neutralizing antibodies to native erythropoietin has been observed in patients treated with recombinant erythropoietins. This has been reported predominantly in patients with CRF. PRCA has been reported in a limited number of subjects exposed to other recombinant erythropoietin products prior to exposure to Aranesp™ therefore, the contribution of Aranesp™ to the development of PRCA is unclear. Any patient with loss of response to Aranesp™ should be evaluated for the etiology of loss of effect (See *PRECAUTIONS: General*). Aranesp™ should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of binding and neutralizing antibodies to Aranesp™, native erythropoietin, and any other recombinant erythropoietin administered to the patient. Amgen may be contacted to assist in this evaluation. In patients with PRCA secondary to neutralizing antibodies to erythropoietin, Aranesp™ should not be administered.

Albumin (Human)

Aranesp™ is supplied in 2 formulations with different excipients, one containing polysorbate 80 and another containing albumin (human), a derivative of human blood (see *DESCRIPTION*). Based on effective donor screening and product manufacturing processes, Aranesp™ formulated with albumin carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

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PRECAUTIONS

General

The safety and efficacy of Aranesp™ therapy have not been established in patients with underlying hematologic diseases (e.g., hemolytic anemia, sickle cell anemia, thalassemia, porphyria).

Lack or Loss of Response to Aranesp™

A lack of response or failure to maintain a hemoglobin response with Aranesp™ doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid or vitamin B_{12} should be excluded or corrected. Depending on the clinical setting, intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, hemolysis, severe aluminum toxicity, and bone marrow fibrosis may compromise an erythropoietic response. In the absence of another etiology, the patient should be evaluated for evidence of pure red cell aplasia and sera should be tested for the presence of antibody to recombinant erythropoietins.

Hematology

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Aranesp™ before adjusting the dose. Because of the time required for erythropoiesis and the red cell half-life, an interval of 2 to 6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hemoglobin.

In order to prevent the hemoglobin from exceeding the recommended target (12 g/dL) or rising too rapidly (greater than 1.0 g/dL in 2 weeks), the guidelines for dose and frequency of dose adjustments should be followed (see *WARNINGS, DOSAGE AND ADMINISTRATION: Dose Adjustment*).

Allergic Reactions

There have been rare reports of potentially serious allergic reactions including skin rash and urticaria associated with Aranesp™. Symptoms have recurred with rechallenge, suggesting a causal relationship exists in some instances. If a serious allergic or anaphylactic reaction occurs, Aranesp™ should be immediately and permanently discontinued and appropriate therapy should be administered.

Patients With CRF Not Requiring Dialysis

Patients with CRF not yet requiring dialysis may require lower maintenance doses of Aranesp™ than patients receiving dialysis. Though predialysis patients generally receive less frequent monitoring of blood pressure and laboratory parameters than dialysis patients, predialysis patients may be more responsive to the effects of Aranesp™, and

require judicious monitoring of blood pressure and hemoglobin. Renal function and fluid and electrolyte balance should also be closely monitored.

Dialysis Management

Therapy with Aranesp™ results in an increase in RBCs and a decrease in plasma volume, which could reduce dialysis efficiency; patients who are marginally dialyzed may require adjustments in their dialysis prescription.

Growth Factor Potential

Aranesp™ is a growth factor that primarily stimulates RBC production. The possibility that Aranesp™ can act as a growth factor for any tumor type, particularly myeloid malignancies, has not been evaluated. In the randomized, placebo-controlled study in 314 subjects with advanced lung cancer, there were no statistically significant differences in time-to-progression (TTP) or overall survival (OS) observed, however the study was not designed to detect or exclude clinically meaningful differences in either TTP or OS.

Laboratory Tests

After initiation of Aranesp™ therapy, the hemoglobin should be determined weekly until it has stabilized and the maintenance dose has been established (see *DOSAGE AND ADMINISTRATION*). After a dose adjustment, the hemoglobin should be determined weekly for at least 4 weeks until it has been determined that the hemoglobin has stabilized in response to the dose change. The hemoglobin should then be monitored at regular intervals.

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients before and during treatment, as the majority of patients will eventually require supplemental iron therapy. Supplemental iron therapy is recommended for all patients whose serum ferritin is below 100 mcg/L or whose serum transferrin saturation is below 20%.

Information for Patients

Patients should be informed of the possible side effects of Aranesp™ and be instructed to report them to the prescribing physician. Patients should be informed of the signs and symptoms of allergic drug reactions and be advised of appropriate actions. Patients should be counseled on the importance of compliance with their Aranesp™ treatment, dietary and dialysis prescriptions, and the importance of judicious monitoring of blood pressure and hemoglobin concentration should be stressed.

If it is determined that a patient can safely and effectively administer Aranesp™ at home, appropriate instruction on the proper use of Aranesp™ should be provided for patients and their caregivers, including careful review of the “Information for Patients and Caregivers” insert. Patients and caregivers should also be cautioned against the reuse of needles, syringes, or drug product, and be thoroughly instructed in their proper disposal.

A puncture-resistant container for the disposal of used syringes and needles should be made available to the patient.

Drug Interactions

No formal drug interaction studies of Aranesp™ have been performed.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity: The carcinogenic potential of Aranesp™ has not been evaluated in long-term animal studies. Aranesp™ did not alter the proliferative response of non-hematological cells *in vitro* or *in vivo.* In toxicity studies of approximately 6 months duration in rats and dogs, no tumorigenic or unexpected mitogenic responses were observed in any tissue type. Using a panel of human tissues, the *in vitro* tissue binding profile of Aranesp™ was identical to Epoetin alfa. Neither molecule bound to human tissues other than those expressing the erythropoietin receptor.

Mutagenicity: Aranesp™ was negative in the *in vitro* bacterial and CHO cell assays to detect mutagenicity and in the *in vivo* mouse micronucleus assay to detect clastogenicity.

Impairment of Fertility: When administered intravenously to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected at any doses evaluated (up to 10 mcg/kg/dose, administered 3 times weekly). An increase in post implantation fetal loss was seen at doses equal to or greater than 0.5 mcg/kg/dose, administered 3 times weekly.

Pregnancy Category C

When Aranesp™ was administered intravenously to rats and rabbits during gestation, no evidence of a direct embryotoxic, fetotoxic, or teratogenic outcome was observed at doses up to 20 mcg/kg/day. The only adverse effect observed was a slight reduction in fetal weight, which occurred at doses causing exaggerated pharmacological effects in the dams (1 mcg/kg/day and higher). No deleterious effects on uterine implantation were seen in either species. No significant placental transfer of Aranesp™ was observed in rats. An increase in post implantation fetal loss was observed in studies assessing fertility (see *PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility: Impairment of Fertility*).

Intravenous injection of Aranesp™ to female rats every other day from day 6 of gestation through day 23 of lactation at doses of 2.5 mcg/kg/dose and higher resulted in offspring (F1 generation) with decreased body weights, which correlated with a low incidence of deaths, as well as delayed eye opening and delayed preputial separation. No adverse effects were seen in the F2 offspring.

There are no adequate and well-controlled studies in pregnant women. Aranesp™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether Aranesp™ is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Aranesp™ is administered to a nursing woman.

Pediatric Use

The safety and efficacy of Aranesp™ in pediatric patients have not been established.

Geriatric Use

Of the 1598 CRF patients in clinical studies of Aranesp™, 42% were age 65 and over, while 15% were 75 and over. Of the 873 cancer patients in clinical studies receiving Aranesp™ and concomitant chemotherapy, 45% were age 65 and over, while 14% were 75 and over. No overall differences in safety or efficacy were observed between older and younger patients.

ADVERSE REACTIONS

General

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Aranesp™ cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

Chronic Renal Failure Patients

In all studies, the most frequently reported serious adverse reactions with Aranesp™ were vascular access thrombosis, congestive heart failure, sepsis, and cardiac arrhythmia. The most commonly reported adverse reactions were infection, hypertension, hypotension, myalgia, headache and diarrhea, (see *WARNINGS: Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin/Hypertension*). The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Aranesp™, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were hypotension, hypertension, fever, myalgia, nausea, and chest pain.

The data described below reflect exposure to Aranesp™ in 1598 CRF patients, including 675 exposed for at least 6 months, of whom 185 were exposed for greater than 1 year. Aranesp™ was evaluated in active-controlled (n = 823) and uncontrolled studies (n = 775).

The rates of adverse events and association with Aranesp™ are best assessed in the results from studies in which Aranesp™ was used to stimulate erythropoiesis in patients anemic at study baseline (n = 348), and, in particular, the subset of these patients in randomized controlled trials (n = 276). Because there were no substantive differences in

the rates of adverse reactions between these subpopulations, or between these subpopulations and the entire population of patients treated with Aranesp™, data from all 1598 patients were pooled.

The population encompassed an age range from 18 to 91 years. Fifty-seven percent of the patients were male. The percentages of Caucasian, Black, Asian, and Hispanic patients were 83%, 11%, 3%, and 1%, respectively. The median weekly dose of Aranesp™ was 0.45 mcg/kg (25^{th}, 75^{th} percentiles: 0.29, 0.66 mcg/kg).

Some of the adverse events reported are typically associated with CRF, or recognized complications of dialysis, and may not necessarily be attributable to Aranesp™ therapy. No important differences in adverse event rates between treatment groups were observed in controlled studies in which patients received Aranesp™ or other recombinant erythropoietins.

The data in *Table 1* reflect those adverse events occurring in at least 5% of patients treated with Aranesp™.

Table 1. Adverse Events Occurring in ³ 5% of CRF Patients

Event	Patients Treated With Aranesp™ (n = 1598)
APPLICATION SITE	
Injection Site Pain	7%
BODY AS A WHOLE	
Peripheral Edema	11%
Fatigue	9%
Fever	9%
Death	7%
Chest Pain, Unspecified	6%
Fluid Overload	6%
Access Infection	6%
Influenza-like Symptoms	6%
Access Hemorrhage	6%
Asthenia	5%
CARDIOVASCULAR	
Hypertension	23%
Hypotension	22%
Cardiac Arrhythmias/Cardiac Arrest	10%
Angina Pectoris/Cardiac Chest Pain	8%
Thrombosis Vascular Access	8%
Congestive Heart Failure	6%
CNS/PNS	
Headache	16%
Dizziness	8%
GASTROINTESTINAL	
Diarrhea	16%
Vomiting	15%
Nausea	14%
Abdominal Pain	12%
Constipation	5%
MUSCULO-SKELETAL	
Myalgia	21%
Arthralgia	11%
Limb Pain	10%
Back Pain	8%

(Continued)

Table 1. Adverse Events Occurring in ³ 5% of CRF Patients (Continued)

Event	Patients Treated With Aranesp™ (n = 1598)
RESISTANCE MECHANISM	
Infection[a]	27%
RESPIRATORY	
Upper Respiratory Infection	14%
Dyspnea	12%
Cough	10%
Bronchitis	6%
SKIN AND APPENDAGES	
Pruritus	8%

[a] Infection includes sepsis, bacteremia, pneumonia, peritonitis, and abscess.

The incidence rates for other clinically significant events are shown in *Table 2*.

Table 2. Percent Incidence of Other Clinically Significant Events in CRF Patients

Event	Patients Treated With Aranesp™ (n = 1598)
Acute Myocardial Infarction	2%
Seizure	1%
Stroke	1%
Transient Ischemic Attack	1%

Thrombotic Events

Vascular access thrombosis in hemodialysis patients occurred in clinical trials at an annualized rate of 0.22 events per patient year of Aranesp™ therapy. Rates of thrombotic events (e.g., vascular access thrombosis, venous thrombosis, and pulmonary emboli) with Aranesp™ therapy were similar to those observed with other recombinant erythropoietins in these trials; the median duration of exposure was 12 weeks.

Cancer Patients Receiving Chemotherapy

The data described below reflect the exposure to Aranesp™ in 873 cancer patients. Aranesp™ was evaluated in seven studies that were active-controlled and/or placebo-controlled studies of up to 6 months duration. The Aranesp™ treated patient demographics were as follows: median age of 63 years (range of 20 to 91 years);

40% male; 88% Caucasian, 5% Hispanic, 4% Black, and 3% Asian. Over 90% of patients had locally advanced or metastatic cancer, with the remainder having early stage disease. Patients with solid tumors (e.g., lung, breast, colon, ovarian cancers), and lymphoproliferative malignancies (e.g., lymphoma, multiple myeloma) were enrolled in the clinical studies. All of the 873 Aranesp™ treated subjects also received concomitant cyclic chemotherapy.

The most frequently reported serious adverse events included death (10%), fever (4%), pneumonia (3 %), dehydration (3%), vomiting (2%), and dyspnea (2%). The most commonly reported adverse events were fatigue, edema, nausea, vomiting, diarrhea, fever and dyspnea (see *Table 3*). Except for those events listed in *Tables 3 and 4*, the incidence of adverse events in clinical studies occurred at a similar rate compared with patients who received placebo and were generally consistent with the underlying disease and its treatment with chemotherapy. The most frequently reported reasons for discontinuation of Aranesp™ were progressive disease, death, discontinuation of the chemotherapy, asthenia, dyspnea, pneumonia, and gastrointestinal hemorrhage. No important differences in adverse event rates between treatment groups were observed in controlled studies in which patients received Aranesp™ or other recombinant erythropoietins.

Table 3. Adverse Events Occurring in ³ 5% of Patients Receiving Chemotherapy

Event	Aranesp™ (n = 873)	Placebo (n = 221)
BODY AS A WHOLE		
Fatigue	33%	30%
Edema	21%	10%
Fever	19%	16%
CNS/PNS		
Dizziness	14%	8%
Headache	12%	9%
GASTROINTESTINAL		
Diarrhea	22%	12%
Constipation	18%	17%
METABOLIC/NUTRITION		
Dehydration	5%	3%
MUSCULO-SKELETAL		
Arthalgia	13%	6%
Myalgia	8%	5%
SKIN AND APPENDAGES		
Rash	7%	3%

Table 4. Incidence of Other Clinically Significant Adverse Events in Patients Receiving Chemotherapy

Event	All Aranesp™ (n = 873)	Placebo (n = 221)
Hypertension	3.7%	3.2%
Seizures/Convulsions	0.6%	0.5%
Thrombotic Events	6.2%	4.1%
Pulmonary Embolism	1.3%	0.0%
Thrombosis	5.6%	4.1%

Seizures/Convulsions include the preferred terms: Convulsions, Convulsions Grand Mal, and Convulsions Local.
Thrombosis includes: Thrombophlebitis, Thrombophlebitis Deep, Thrombosis Venous, Thrombosis Venous Deep, Thromboembolism, and Thrombosis

Thrombotic and Cardiovascular Events

Overall, the incidence of thrombotic events was 6.2% for Aranesp™ and 4.1% for placebo. However, the following events were reported more frequently in Aranesp-treated patients than in placebo-controls: pulmonary embolism, thromboembolism, thrombosis, and thrombophlebitis (deep and/or superficial). In addition, edema of any type was more frequently reported in Aranesp-treated (21%) patients than in patients who received placebo (10%).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Aranesp™ has not been adequately determined. Radioimmunoprecipitation assays were performed on sera from 1534 CRF and 833 cancer patients treated with Aranesp™ in clinical studies. High-titer antibodies were not detected in patients with CRF, but assay sensitivity may be inadequate to reliably detect lower titers. Antibodies were detected by radioimmunoprecipitation in sera from three cancer patients; neutralizing activity, possibly related to antibodies, was detected in one of these three patients. There was no evidence of PRCA in that patient. (see *WARNINGS: Pure Red Cell Aplasia*).

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the

incidence of antibodies to Aranesp™, with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

The maximum amount of Aranesp™ that can be safely administered in single or multiple doses has not been determined. Doses over 3.0 mcg/kg/week for up to 28 weeks have been administered to CRF patients. Doses up to 8.0 mcg/kg every week and 15.0 mcg/kg every 3 weeks have been administered to cancer patients for up to 12-16 weeks. Excessive rise and rate of rise in hemoglobin concentration, however, have been associated with adverse events (see *WARNINGS* and *DOSAGE AND ADMINISTRATION: Dose Adjustment*). In the event of polycythemia, Aranesp™ should be temporarily withheld (see *DOSAGE AND ADMINISTRATION: Dose Adjustment*). If clinically indicated, phlebotomy may be performed.

DOSAGE AND ADMINISTRATION

General

IMPORTANT: AranespÔ dosing regimens are different for each of the indications described in this section of the package insert. Due to the longer serum half-life, AranespÔ should be administered less frequently than Epoetin alfa (for example where Epoetin alfa is administered three times a week, Aranespä should be administered weekly). Aranespä should be administered under the supervision of a healthcare professional.

Chronic Renal Failure Patients

Aranesp™ is administered either IV or SC as a single weekly injection. The dose should be started and slowly adjusted as described below based on hemoglobin levels. If a patient fails to respond or maintain a response, other etiologies should be considered and evaluated (see *PRECAUTIONS: General/Laboratory Tests*). When Aranesp™ therapy is initiated or adjusted, the hemoglobin should be followed weekly until stabilized and monitored at least monthly thereafter.

For patients who respond to Aranesp™ with a rapid increase in hemoglobin (e.g., more than 1.0 g/dL in any 2-week period), the dose of Aranesp™ should be reduced (see *DOSAGE AND ADMINISTRATION: Dose Adjustment* because of the association of excessive rate of rise of hemoglobin with adverse events (see *WARNINGS: Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin*).

The dose should be adjusted for each patient to achieve and maintain a target hemoglobin level not to exceed 12 g/dL.

Starting Dose

Correction of Anemia

The recommended starting dose of Aranesp™ for the correction of anemia in CRF patients is 0.45 mcg/kg body weight, administered as a single IV or SC injection once weekly. Because of individual variability, doses should be titrated to not exceed a target hemoglobin concentration of 12 g/dL (see Dose Adjustment). For many patients, the appropriate maintenance dose will be lower than this starting dose. Predialysis patients, in particular, may require lower maintenance doses. Also, some patients have been treated successfully with a SC dose of Aranesp™ administered once every 2 weeks.

Conversion From Epoetin alfa to Aranespä

The starting weekly dose of Aranesp™ should be estimated on the basis of the weekly Epoetin alfa dose at the time of substitution (see *Table 5*). Because of individual variability, doses should then be titrated to maintain the target hemoglobin. Due to the longer serum half-life, Aranesp™ should be administered less frequently than Epoetin alfa. Aranesp™ should be administered once a week if a patient was receiving Epoetin alfa 2 to 3 times weekly. Aranesp™ should be administered once every 2 weeks if a patient was receiving Epoetin alfa once per week. The route of administration (IV or SC) should be maintained.

Table 5. Estimated AranespÔ Starting Doses (mcg/week) Based on Previous Epoetin alfa Dose (Units/week)

Previous Weekly Epoetin alfa Dose (Units/week)	Weekly Aranesp™ Dose (mcg/week)
< 2500	6.25
2500 to 4999	12.5
5000 to 10,999	25
11,000 to 17,999	40
18,000 to 33,999	60
34,000 to 89,999	100
≥ 90,000	200

Dose Adjustment

The dose should be adjusted for each patient to achieve and maintain a target hemoglobin not to exceed 12 g/dL.

Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by

approximately 25%. If the hemoglobin continues to increase, doses should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the hemoglobin increases by more than 1.0 g/dL in a 2-week period, the dose should be decreased by approximately 25%.

If the increase in hemoglobin is less than 1.0 g/dL over 4 weeks and iron stores are adequate (see *PRECAUTIONS: Laboratory Tests*), the dose of Aranesp™ may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

Maintenance Dose

Aranesp™ dosage should be adjusted to maintain a target hemoglobin not to exceed 12 g/dL. If the hemoglobin exceeds 12 g/dL, the dose may be adjusted as described above. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each patient.

Cancer Patients Receiving Chemotherapy

The recommended starting dose for Aranesp™ is 2.25 mcg/kg administered as a weekly SC injection.

The dose should be adjusted for each patient to achieve and maintain a target hemoglobin. If there is less than a 1.0 g/dL increase in hemoglobin after 6 weeks of therapy, the dose of Aranesp™ should be increased up to 4.5 mcg/kg. If hemoglobin increases by more than 1.0 g/dL in a 2-week period or if the hemoglobin exceeds 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin exceeds 13 g/dL, doses should be temporarily withheld until the hemoglobin falls to 12 g/dL. At this point, therapy should be reinitiated at a dose approximately 25% below the previous dose.

Preparation and Administration of Aranesp

Do not shake Aranesp™. Vigorous shaking may denature Aranesp™, rendering it biologically inactive.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.

Do not dilute Aranesp™.

Do not administer Aranesp™ in conjunction with other drug solutions.

Aranesp™ is packaged in single-use vials and contains no preservative. Discard any unused portion. **Do not pool unused portions**.

See the accompanying "Information for Patients and Caregivers" leaflet for complete instructions on the preparation and administration of Aranesp™ for patients.

HOW SUPPLIED

Aranesp™ is available in 2 solutions, an albumin solution and a polysorbate solution. The words "Albumin Free" appear on the polysorbate container labels and the package main panels as well as other panels as space permits. Aranesp™ is available in the following packages:

Single-dose Vial, Polysorbate Solution

1 Vial/Pack, 4 Packs/Case	**4 Vials/Pack, 10 Packs/Case**
200 mcg/1 mL (NDC 55513-006-01)	25 mcg/1 mL (NDC 55513-002-04)
	40 mcg/1 mL (NDC 55513-003-04)
	60 mcg/1 mL (NDC 55513-004-04)
	100 mcg/1 mL (NDC 55513-005-04)

Single-dose Vial, Albumin Solution

1 Vial/Pack, 4 Packs/Case	**4 Vial/Pack, 4 Packs/Case**	**4 Vials/Pack, 10 Packs/Case**
200 mcg/1 mL (NDC 55513-014-01)	200 mcg/1 mL (NDC 55513-014-04)	25 mcg/1 mL (NDC 55513-010-04)
300 mcg/1 mL (NDC 55513-015-01)	300 mcg/1 mL (NDC 55513-015-04)	40 mcg/1 mL (NDC 55513-011-04)
500 mcg/1 mL (NDC 55513-016-01)		60 mcg/1 mL (NDC 55513-012-04)
		100 mcg/1 mL (NDC 55513-013-04)
		150 mcg/0.75 mL (NDC 55513-054-04)

Storage

Store at 2° to 8° C (36° to 46° F). Do not freeze or shake. Protect from light.

REFERENCES

1. Egrie JC and Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). *Brit J Cancer*. 2001;84(suppl 1):3-10.
2. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998;339:584-90.

Rx only

This product, or its use, may be covered by one or more US Patents, including US Patent No. 5,618,698, in addition to others including patents pending.

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